

Hereditary anemias in Hawaii: An update

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Since our first report was published in the Hawaii Medical Journal in the September 1987 issue and was reprinted in the September 1991 special sesquicentennial issue, with the support of doctors in Hawaii and their referrals, our small team has now tested 5,000 people¹. DNA analyses have been completed in over 1,000 people.

In this hereditary anemia project, many families have benefited; every participant has been sent a personalized report. We have learned valuable lessons about the attitudes and cultures of participants¹⁵⁻¹⁸ about the hematological and clinical features of the diverse thalassemias prevalent in Southeast Asians^{1, 3, 4, 7-12}; about how best to detect these and how DNA analyses help in confirming or revising diagnoses^{4, 5, 7, 9, 10, 12}. Couples at risk for having severely affected children have been counseled, pregnancies at-risk have been tested⁶.

The α -thalassemias have major health implications especially for Filipinos who are the most rapidly growing ethnic minority throughout the United States⁹.

A special Thalassemia clinic has been established under R Wilkinson MD to provide structured care for transfusion-dependent patients who may need iron-chelation therapy. We showed that Hb H disease from loss of 3 α -globin genes is usually benign, but Hb H/Constant Spring tends to be transfusion-dependent¹¹.

Data from this project have greatly improved knowledge about the ranges and confidence limits of red cell indices for each diagnostic category, with improved interpretations of individual results. Extensive experience has been gained in using red cell indices and isoelectric focusing to detect α and β thalassemia carriers in adults and infants^{1, 7, 10, 12}.

Thalassemia incidences in Laotians and Filipinos were calculated far more accurately than had been done previously³.

Red cell distribution width and red cell zinc protoporphyrin by microfluorimetry are shown to be a reliable inexpensive way to screen for iron deficiency, except for some overlap with β -thalassemia heterozygotes and HB H disease cases.

Innovative DNA techniques have been created, including the first reliable method to look for the Constant Spring mutation⁶. This uses the polymerase chain reaction (PCR) to ampli-

fy DNA from the tail end of the α_2 -globin gene a million-fold in a few hours. The technique has been applied to analyze a few strands of hair sent from patients in India.

We have also devised a novel PCR technique to detect the most common type of single α -globin gene deletion, introducing a strategy that is applicable to any large DNA deletion².

For rapid fetal detection of α -globin deletions, we have developed a multiplex PCR technique to amplify the β -globin, α_1 and α_2 globin genes simultaneously from drops of blood or a few fetal cells. This can be completed in one working day⁸.

We have adopted 2 useful techniques developed by others. One screens for the most common double α -globin deletion, using a monoclonal anti- ζ antibody on a drop of blood^{13, 14}. Another uses denaturing gradient gel electrophoresis to define the dozens of mutations in the β -gene that produce the β -thalassemias.

Data from this project have been presented in national and international conferences^{1-5, 7-10, 12-18}; several articles have been published^{4, 7, 10-13, 16-18} and more are being prepared. I was the coordinator and chair of a special workshop on thalassemia screening at the Eighth International Congress on Human Genetics in Washington, DC, in October, 1991.

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Medical Genetic Services

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AXID[®] nizatidine capsules

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*—for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

Contraindication: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H₂-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

Precautions: General—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix[®] may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chloridazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since marker introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H₂-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

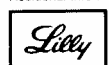
Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H₂-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method. PV 2093 AMP [101591]

Additional information available to the profession on request.



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HEREDITARY ANEMIA (Continued from page 17)

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mission. Intellectual property protection must be strengthened, not weakened as in Canada, and tough action taken against patent pirates.

- **Cut product liability costs.** The high cost of protecting against the possibility of high jury awards in product liability cases adds millions of dollars to drug costs. A reform of the tort laws is needed, including protection against punitive damages for products that have been deemed safe and effective by the Food and Drug Administration.

Conclusion

The Senate Aging Committee's staff is singling out one competitive industry for price controls and weakened patent protection. If their recommendations are enacted, it would have a damaging effect on both health care and U.S. international competitiveness.

